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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,019	GIESING ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _15 September 2008_.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _1-4,6,11,12 and 14-25_ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _1-4,6,11,12 and 14-25_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _2/18/2005_ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☒ Other: _Exhibits I and II_.

DETAILED ACTION

This action is in response to the amendment, filed 9/15/2008, in which claims 5, 7, 9, 10 and 13 were canceled, claims 1-4, 6, 11 and 14-17 were amended, and claims 18-25 were newly added. Claims 1-4, 6, 11, 12 and 14-25 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group I with traverse in the reply filed on 1/28/2008. The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4, 6, 11, 12 and 14-25 are under consideration.

Claim Objections

Claim 1 is objected to because of the following informalities: the phrase "presence of" is duplicated in the penultimate line of the claim. Claims 2-4, 6, 11, 12 and 14-25 depend from claim 1 and thus are objected to for the same reason applied to claim 1. Appropriate correction is required. This is a new objection, necessitated by the amendment of claim 1 in the reply filed 9/15/2008.

Claim 21 is objected to because of the following informalities: the phrase "amino acid sequences" should be changed to "amino acid sequence" to improve the grammar of the claim.

Appropriate correction is required. This is a new objection, necessitated by the addition of new claim 21 in the reply filed 9/15/2008.

Claim 23 is objected to because of the following informalities: the phrase "amino acid sequences" should be changed to "amino acid sequence" to improve the grammar of the claim. Appropriate correction is required. This is a new objection, necessitated by the addition of new claim 23 in the reply filed 9/15/2008.

Response to Arguments - Claim Objections

The previous objection of claims 1-7 and 11-17 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 9/15/2008.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection, necessitated by the addition of new claims 23 and 24 in the reply filed 9/15/2008.

Claim 23 recites the limitation "the human glutathione peroxidase 1 gene" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Claim 23 depends from claim 1, which requires a "glutathione peroxidase 1 gene." Claim 1 encompasses glutathione peroxidase 1 genes from any species, and does not explicitly or inherently limit the gene to a

human gene. Claim 23 requires the gene to encode a protein having "an amino acid sequence" (two or more contiguous amino acids) as set forth in SEQ ID NO: 17 or an allelic variant thereof. Thus, the sequence of claim 23 is not limited to a protein encoded by a human gene. It is unclear if claim 23 is limited to a human gene.

Claim 24 recites the limitation "the human glutathione peroxidase gene" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Claim 24 depends from claim 1, which requires a "glutathione peroxidase 1 gene." Claim 1 encompasses glutathione peroxidase 1 genes from any species, and does not explicitly or inherently limit the gene to a human gene. Claim 24 requires the gene to encode an mRNA which is capable of being amplified using the primer sequences set forth in SEQ ID NO: 7 and SEQ ID NO: 8. These sequences are not specific to humans. See the attached alignments in Exhibits I and II. It is unclear if claim 24 is limited to a human gene.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 11, 12 and 14-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (a) obtaining a blood sample from a human subject, collecting mononuclear cells from the blood sample, removing a fraction of the mononuclear cells to obtain test fraction A’, passing the remaining mononuclear cells through a screen with a 20 μm mesh, and collecting cells from the mesh to obtain test fraction C;

(b) obtaining blood samples from a healthy human subjects not suffering from cancer, collecting mononuclear cells from the blood samples, removing a fraction of the mononuclear cells to obtain reference fraction A’, passing the remaining mononuclear cells through a screen with a 20 μm mesh, and collecting cells from the mesh to obtain reference fraction C;

(c) isolating CD45-positive lymphocytes from reference fraction A’ to obtain reference fraction A,

(d) isolating mRNA from test fraction A’, test fraction C, reference fraction A, and reference fraction C;

(e) measuring the expression level of manganese superoxide dismutase (MNSOD), thioredoxin reductase (TXNRD1), and glutathione peroxidase (GPX1) in each of the mRNA samples, wherein said measuring is by reverse transcription and PCR using primers consisting of SEQ ID NOs: 1 and 2 for MNSOD, SEQ ID NOs: 4 and 5 for TXNRD1, and SEQ ID NOs: 7 and 8 for GPX1;

(f) measuring the expression level of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in each of the mRNA samples;

(g) calculating for each mRNA sample the ratio of each of MNSOD, TXNRD1, and GPX1 expression to GAPDH expression;

(h) determining the average and standard deviation for the expression ratio of MNSOD, TXNRD1, and GPX1 from reference fraction C to reference fraction A for the healthy control samples, and determining a limit for expression which is the average plus one standard deviation;

(i) determining the expression ratio of MNSOD, TXNRD1, and GPX1 from test fraction C to test fraction A' of the test sample; and

(j) comparing the expression ratio for each of MNSOD, TXNRD1, and GPX1 for the test sample to the determined limit for each gene;

wherein an expression ratio higher than the limit for at least one of MNSOD, TXNRD1 or GPX1 indicates that disseminated cancer cells are present in the test blood sample, does not reasonably provide enablement for the use of any body fluid from any species of organism, the absence of a reference sample, the use of any reference sample, determining the expression of any manganese superoxide dismutase gene, any thioredoxin reductase gene, or any glutathione peroxidase gene, diagnosis of a tumor, or estimating the risk to develop a metastasis or recurrence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection was made in the Office action mailed 5/15/2008 and has been rewritten to address the amendments to the claims in the reply filed 9/15/2008.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to a method for investigating a body fluid for cancer cells, comprising (a) obtaining a cell-containing fraction from the body fluid with enrichment of cancer cells and determining in the cell-containing fraction the expression of at least two genes which are selected from the group consisting of (i) manganese superoxide dismutase genes; (ii) thioredoxin reductase 1 genes; and (iii) glutathione peroxidase 1 genes; (b)

providing a further cell-containing fraction of the body fluid or of a comparable biological sample and determining the expression of the genes in the further cell-containing fraction; and (c) comparing the expression fro each gene in the cell-containing fraction with its expression in the further cell-containing fraction, wherein the body fluid is selected from blood and bone marrow and an elevated expression of each gene determined in the cell-containing fraction as compared to its expression in the further cell-containing fraction indicates the presence of disseminated cancer cells in the body fluid. Claim 2 requires at least one manganese superoxide dismutase gene, at least one thioredoxin reductase 1 gene, and at least one glutathione peroxidase 1 gene to be determined. Claim 11 requires the expression of at least one manganese superoxide dismutase gene and at least one further gene selected from the group consisting of thioredoxin reductase 1 genes and glutathione peroxidase 1 genes to be determined. Claim 3 limits the body fluid to blood. Claim 4 limits the enrichment of the cancer cells to passing the body fluid or parts thereof through a screen with a mesh or pore width of about 10 to 200 μm and obtaining the cell fraction retained on the screen. Claim 6 further limits comparable biological sample to one that is derived from the individual whose body fluid is investigated for cancer cells. Claim 18 limits the genes to human genes. Claim 19 limits the manganese superoxide dismutase gene to a gene that encodes a protein having an amino acid sequence as set forth in SEQ ID NO: 13 or an allelic variant thereof. Claim 20 requires the superoxide dismutase gene to encode an mRNA which is capable of being amplified using the primer sequences as set forth in SEQ ID NO: 1 and SEQ ID NO: 2. Claim 21 requires the thioredoxin reductase 1 gene to encode a protein having an amino acid sequence as set forth in SEQ ID NO: 15 or an allelic variant thereof. Claim 22 requires the thioredoxin reductase gene to encode an mRNA that is capable of being amplified

using the primer sequences set forth in SEQ ID NOS: 4 and 5. Claim 23 requires the glutathione peroxidase 1 gene to encode a protein having an amino acid sequence as set forth in SEQ ID NO: 17 or an allelic variant thereof. Claim 24 requires the glutathione peroxidase gene to encode an mRNA that is capable of being amplified using the primer sequences set forth in SEQ ID NOS: 7 and 8. Claim 25 requires determining mRNA expression.

Claims 12-17 are directed to the intended uses of the method. Claim 12 indicates that the method is for identifying disseminated cancer cells in the body fluid. Claim 14 indicates that the method is for diagnosis of a tumor. Claim 15 indicates that the method is for identifying the presence of a tumor. Claim 16 indicates that the method is for estimating the risk to develop metastasis or a recurrence. Claim 17 indicates that the elevated expression of at least one gene indicates a risk to develop a metastasis or recurrence.

The nature of the invention is complex in that carrying out the recited method steps must enable the intended uses of the method, including identifying disseminated cancer cells in a body fluid, providing a diagnosis of a tumor, and estimating the risk to develop a metastasis or recurrence.

Breadth of the claims: The claims are broad in that the specification defines the term "cancer cell" to mean a cell which exhibits one or more modifications associated with cancer, i.e., dysplasia in the general sense. The term is defined to specifically include precursors of cancer and tumor cells with cancerous or tumorous modifications (e.g., page 4, lines 6-19).

The claims are very broad in that they encompass determining the expression of at least two genes selected from manganese superoxide dismutase genes, thioredoxin reductase 1 genes, and glutathione peroxidase 1 genes. The specification defines the term "manganese superoxide

dismutase (MNSOD)" to mean enzymes which catalyze the decomposition of superoxide free radicals to form hydrogen peroxide, and in particular the enzymes which constitute enzyme class 1.15.1.1 (paragraph bridging pages 14-15). The enzymes of this class are not limited to manganese-containing superoxide dismutase enzymes (See the entry for 1.15.1.1 from the Enzyme nomenclature databases, accessed from http://us.expasy.org/enzyme). Enzymes of the class 1.15.11 include all superoxide dismutase enzymes, including iron or manganese or copper and zinc superoxide dismutase. Thus, the claims read on determining the expression level of any superoxide dismutase enzyme from any species of organism from which a body fluid may be obtained. The claims read on determining the expression level of any thioredoxin reductase 1 isoform from any species of organism from which blood or bone marrow may be obtained. The claims read on determining the expression level of any glutathione peroxidase isoform from any species of organism from which blood or bone marrow may be obtained. Accordingly, the claims broadly encompass obtaining blood or bone marrow from any species of organism, and determining the expression of at least two of the broadly defined classes of genes selected from the genus of manganese superoxide dismutase genes, the genus of thioredoxin reductase 1 genes, and the genus of glutathione peroxidase 1 genes. It is noted that claims 19, 31 and 23 are directed to "an amino acid sequence" of the recited sequence identifiers, and, thus, do not require more than two contiguous amino acids of the sequence recited in the claims. Further, claims 20, 22 and 24 do not require the use of the primers in the claimed method. The gene must only be capable of being amplified by the primer sets. As shown in Exhibits I and II, the primers of SEQ ID NOS: 7 and 8 are capable of amplifying genes from a number of different species.

The claims are broad in that the comparable biological sample may be from any body fluid or solid tissue of any subject. Accordingly, the claims encompass a large number of different comparisons between the tested cell-containing fraction and a second cell-containing fraction or a comparable biological sample.

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification envisions using a method for investigating body fluids for cancer cells to permit reliable tumor diagnosis and prognosis (e.g., page 1, lines 5-13).

The specification teaches that the prior art shows that some solid tumors and metastases thereof found in solid tissue have increased expression of MNSOD, including colorectal tumors and hepatic metastases thereof, lung tumors, breast cancer cells, stomach tumors, and gliobalastoma (e.g., page 2, lines 5-22). However, the specification also notes that benign hyperplasias of the breast were often found to be strongly positive for MNSOD expression as compared to neoplastic epithelial cells from invasive carcinomas of the breast (e.g., page 2, lines 22-27). Thus, the specification acknowledges that MNSOD levels are not always higher in dysplastic cells as compared to any cell type. The specification teaches that reduced GPX1 expression was observed in imexon-resistant RPM/8226/I myeloma cells (e.g., page 3, lines 10-12). Thus, gene expression may vary depending upon the sensitivity or resistance of the cancer cell to a cancer therapeutic. Further, the specification teaches that disseminated cancer cells are a tumor entity independent of the primary tumor and therefore are fundamentally different from

cells of the primary tumor on the basis of a different genotype and phenotype (e.g., page 3, lines 14-22).

At pages 12-27, the specification provides general guidance directed to measuring expression levels of MNSOD, TXNRD and GPX expression by measuring nucleic acid or protein expression.

At pages 28-30, the specification provides guidance with regard to evaluating the obtained expression levels. The specification teaches that it is particularly important to determine whether expression in the cells of the investigated sample is comparatively elevated (e.g., page 28, lines 1-10). The specification teaches that the comparison usually is with cells in which no cancer-associated modification is to be expected (non-cancer cells, normal cells) (e.g., page 28, lines 10-14). The specification suggests that if cancer cells in body fluids are being tested, then the comparison will be those normally occurring in this body fluid. For the case of blood, the normal cells are white blood cells which can be obtained for example by density gradient centrifugation (e.g., the buffy coat or the MNC fraction) or can be separated by more specific isolation methods (e.g., CD45-positive lymphocytes) (e.g., page 28, lines 14-22). The specification asserts that these samples can also be used as a comparison for body fluids other than blood (e.g., page 28, lines 22-25). At page 29, lines 33-39, the specification states, "The test principle according to the invention is therefore based on determining whether enrichment of cancer cells is associated with a measurable increase in MNSOD, TXNRD and GPX expression. The ratio of the expression measured in the test cell mixture to the expression measured in the comparison cell mixture is decisive." The specification goes on to state, "It will usually be expedient for validation of a particular test system to fix a particular quotient (limit) above which

overexpression is present by definition." (See page 30, lines 1-5). Thus, the step of comparing appears to be critical to the claimed invention. Furthermore, the specification notes that the limit may depend on the cell mixtures used and, in particular, on the obtaining thereof (e.g., page 30, lines 7-8).

With respect to early diagnosis, the specification envisions using sputum/saliva for the early diagnosis of lung tumors; urine for the early diagnosis of prostate and bladder tumors; stool for the early diagnosis of colonic and pancreatic tumors; and blood/bone marrow/lymph for the early diagnosis of all disseminating tumors.

With respect to the prognosis and risk of recurrence, the specification envisions using the method of the invention to classify tumor and estimate risk (e.g., paragraph bridging pages 31-32).

The working examples of the specification are directed to one embodiment that falls within the scope of the instant claims. The examples teach the collection of blood from 9 healthy donors and 47 tumor patients. Breast carcinoma cell line BT474 was used as a reference for MNSOD, TXNRD1, and GPX1 expression. To obtain cancer cell fraction C and comparative fractions A' and B', 10 ml of heparinized blood was centrifuges, and the supernatant plasma was removed. The pelleted cells were resuspended in 12 ml of PBS and subjected to density gradient centrifugation. The mononuclear cell fraction was collected, washed and resuspended in 10 ml of PBS. 1 ml of this cell mixture was removed as a possible reference (comparative fraction A'). The remaining 9 ml of cell mixture was passed via a column through a screen woven from polyester filaments with a 20 μm mesh width, and the flow-through from the screen was collected as a possible reference (cell fraction B'). The column was washed five times with 10

ml of PBS, and the cells trapped on the screen were collected in Trizol® solution (cancer cell fraction C). Comparative fractions A' and B' were further processed by isolating CD45-positive lymphocytes to obtain comparative fractions A and B. Gene expression was analyzed by TaqMan® analysis of mRNA expression using the following primers and probes: SEQ ID NO: 1 (sense primer for MNSOD), SEQ ID NO: 2 (antisense primer for MNSOD), SEQ ID NO: 3 (probe for MNSOD), SEQ ID NO: 4 (sense primer for TXNRD1), SEQ ID NO: 5 (antisense primer for TXNRD1), SEQ ID NO: 6 (probe for TXNRD1), SEQ ID NO: 7 (sense primer for GPX1), SEQ ID NO: 8 (antisense primer for GPX1), SEQ ID NO: 9 (probe for GPX1), SEQ ID NO: 10 (sense probe for GAPDH), SEQ ID NO: 11 (antisense probe for GAPDH), and SEQ ID NO: 12 (probe for GAPDH). The specification refers to the following accession numbers for MNSOD, TXNRD1, and GPX1: M36693, X91247, and M21304, respectively. GAPDH expression was measured for fractions A or A' and C, and the ratio of the expression of each gene is expressed as a quotient. The specification teaches tat overexpression of the relevant mRNA is present if the ratio of the fraction C quotient to the fraction A quotient is more than a limit which is to be experimentally defined. Further, the specification teaches that cell equivalents are based on a cell standard (e.g., cell line BT474), where cDNA from the cell standard is included in the quantitative analysis in the form of serial dilutions and serves as a reference system. The specification teaches the amounts of MNSOD, TXNRD1 and GPX1 mRNA determined in fraction C as compared to fraction A for healthy donors (e.g., Table 1). The specification teaches that for subsequent assessment of the levels of expression measured in tumor patients, levels were regarded as positive if they exceeded the average level in healthy donors (ratio of level in fraction C as compared to fraction A) plus one standard deviation, as

indicated as the limit in Table 1 (e.g., page 45, lines 13-26). MNSOD, TXNRD1 and GPX1 was measured in fractions C and A' obtained from the blood of patients diagnosed with a solid tumor (e.g., page 46, lines 1-8). Comparing the expression ratios from fractions C and A' to the limits disclosed in Table 1, it was determined that 78/90 (87%) patients were positive for increased MNSOD expression, 60/90 (67%) of patients were positive for increased TXNRD1 expression, and 53/86 (62%) of patients were positive for GPX1. At least one gene was positive in 93% of patients. Thus, detecting all three genes has a sensitivity of 93%, while the sensitivity of the individual detections is 87, 67 and 62%, respectively (e.g., page 47, lines 25-30). Comparison between the healthy donors and some of the tumor patients is shown at pages 50-51. The specification teaches the use of this specific method to detect disseminated cancer cells in patients with solid tumors.

The specification does not teach the stage or grade of the cancers at the time blood was drawn. There is no indication that the cancer cells detected by increased expression of MNSOD, TXNRD1 or GPX1 are not a result of advanced metastatic cancer. The specification does not teach the sensitivity of the assay for early, non-metastatic cancer.

With respect to estimating the risk to develop metastasis or recurrence, the specification teaches the comparison between tumor patients with out recurrence and those with recurrence in relation to MNSOD, TXNRD1, and GPX1 expression as discussed above (e.g., pages 52-53). While some statistical differences were observed, the percentages disclosed in Table 7a for carcinoma of the breast and Table 7b for tumor patients, indicates that may not be able to use the expression levels of MNSOD, TXNRD1 and/or GPX1 to reliably classify a single test individual as at risk or not at risk of recurrence.

The specification discloses probes that could be used for microarray analysis of MNSOD, GPX2, GPX3, and TXNRD1 (e.g., page 55). The specification asserts that overexpression of MNSOD and GPX2 is clearly evident upon hybridization of mRNA total amplification from a tumor cell fraction C as compared to cell fraction A' (e.g., page 57 and Figure 1).

The specification does not teach the expression of MNSOD, TXNRD or GPX in body fluids such as bone marrow, lymph, sputum, lavages, puncture fluids, ascites, mucosal smears, exudates, urine or stool. The specification does not contain working examples directed to the diagnosis of a tumor or risk of developing a metastasis.

Predictability and state of the art: The art teaches that gene expression analysis is commonly used for three different purposes: (1) as a screening tool to identify individual genes of interest that might contribute to an important biological function, (2) to obtain insight into an important biological function, and (3) as a classification tool to sort cases into clinically important categories (Pusztai and Hess, Annals of Oncology, Vol. 15, pages 1731-1737, 2004; e.g., paragraph bridging pages 1732-1733). Pusztai and Hess teach that validation of gene expression important to biological function may be validated by using different methods, such as RT-PCR, whereas the most appropriate validation for using gene expression analysis as a classification tool is testing the predictor on independent sets of cases (e.g., page 1733, left column, 1st full paragraph). In the instant case the specification does not teach that the expression levels can be used to reliably categorize an individual. For example, the specification does not teach the classification of individuals as at risk or not at risk to develop a metastasis, or at risk to develop a recurrence.

Further, Shalon et al (US 2001/0051344 A1, Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (e.g., paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (e.g., paragraph [0156]). Pusztai and Hess teach that larger samples sizes may be needed to validate classification tests, and the number of samples will vary depending upon the acceptable error rates, level of inter-patient variability, the size of the difference in mean expression values, and the prevalence of the phenotype among the group being tested (e.g., page 1734, paragraph bridging columns; Table 1).

Genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined (Kroese et al (Genetics in Medicine, Vol. 6, pages. 475-480, 2004). Kroese et al teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (e.g., page 477, 1st column, 1st and 2nd full paragraph). Kroese et al teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are

likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (e.g., page 479, 2nd column, last paragraph).

The prior art reveals that differences in gene expression observed between two groups are do not necessarily provide markers that can be used to reliably classify a subject. Golub et al (Science, Bol. 286, pages 531-537, October 1999) teach the use of a two-step procedure to test the validity of gene expression levels as predictors: step 1 involves cross-validation of the predictors on the initial data set, where one withholds a samples, builds a predictor based only on the remaining samples and predicts the class of the withheld sample; step 2 involves the repetition of assessing the clinical accuracy of the predictor set on an independent set of samples (e.g., page 532, right column). Although Golub et al could detect gene expression differences between chemotherapy responders and non-responders, those differences could not be use to predictably classify individuals (e.g., page 533, paragraph bridging left and middle columns). Accordingly, the art demonstrates the unpredictable nature of extrapolating gene expression differences to a method of class prediction.

The art teaches that different isoforms of MNSOD, TXNRD1 and GPX1 are expressed (See the Entrez Gene entries for SOD2, TXNRD1, and GPX1 downloaded from http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene on 5/5/2008). These genes correspond to the genes detected by the primers recited in the present specification. The specification does not specifically teach the increased expression of each isoform in circulating cancer cells. Thus, it would be unpredictable to detect any isoform of these genes for the use of the claimed method. Moreover, Seven et al (Clinical Biochemistry, Vol. 32, No. 5, pages 369-373, 1999) teach that the constitutive levels and the inducibility of antioxidant enzymes including superoxide

dismutase and glutathione peroxidase vary for different tissues, and the expression of these enzymes may vary according to the type of cancer or tissue studies, resulting in controversy in the literature (e.g., page 372, left column, last two paragraphs). Seven et al did not find an increased amount of CuZn SOD or glutathione peroxidase in the red blood cell fraction of laryngeal cancer patients (e.g., page 372, paragraph bridging columns; Table 1).

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the full scope of the invention is large. One would be required to conduct a large number of experiments to test the expression of many manganese superoxide dismutase genes, thioredoxin reductase 1 genes, and glutathione peroxidase 1 genes, in combinations of two, from cell-containing fractions of body fluid, including blood and bone marrow in a number of different species of organisms. Given the variable expression of the enzymes based upon tumor or cell type and the expression of multiple different isoforms, it would be unpredictable to extrapolate the results of the present specification to the use of any manganese superoxide dismutase gene, any thioredoxin reductase 1 gene, and/or any glutathione peroxidase 1 gene. As discussed in the present specification, the limit used to determine whether a gene is overexpressed must be experimentally determined for each particular comparison. This comparison will be specific for the organism, body fluid, cells collected from the body fluid, gene whose expression is determined, isoform whose expression is determined, whether mRNA or protein expression is measured, the specific method used to measure the mRNA or protein (e.g., RT-PCR, microarray, or ELISA), whether enrichment is used, and the type of control sample. A large amount of unpredictable experimentation would be required to use the full scope of the claimed method to detect the presence of disseminated cancer cells, provide

diagnosis of a tumor, estimate the risk to develop a metastasis, or estimate the risk to develop a recurrence.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1-4, 6, 11, 12 and 14-25 are not considered to be fully enabled by the instant specification.

Response to Amendment – Declaration of Professor Giesing

The declaration under 37 CFR 1.132 filed 9/15/2008 is insufficient to overcome the rejection of claims 1-4, 6, 11, 12 and 14-25 based upon insufficiency of disclosure as set forth in the last Office action. The evidence presented in the declaration is not commensurate in scope with the claims.

The declaration provides experimental data for a study to determine whether a molecular PCR-based detection of disseminated cancer cells in blood can be used in the diagnosis of prostate tumors in humans with a tPSA between 4 to 10 ng/ml and in monitoring disease progression to determine the relapse-free survival and the risk of developing a metastasis or recurrence.

The claims are drawn to the use of a body fluid, which is blood or bone marrow, from a subject of any species of organism with potentially any type of cancer. The experimental evidence presented in the declaration is directed to human blood from subjects at risk of prostate cancer (tPSA between 4 to 10 ng/ml) or subjects with a clinical diagnosis of prostate cancer (e.g., pages 2-3 of declaration and Table I).

In the experiments disclosed in the declaration, mononuclear cells (MNC) were purified from the peripheral blood and passed over a 20 μm polyester mesh (e.g., page 3). The declaration states that large cancer cells are greater than or equal to 20 μm, and cancer cells and cell clusters are retained on the mesh (e.g., page 3). RNA was isolated from total MNC and the cells retained on the mesh, and expression of SOD2, TXNRD1 and GPX1 was determined using the same primers as disclosed in the present specification. The amount of target message was normalized to the level of GAPDH and expressed as relative specific expression (RSE) calculated from the ration of circulating prostate cells and MNC. Normalized reference expression values were calculated as cell equivalents stemming from target enriched reference cell lines and MNC after counting in a Muller chamber. Multiple different isoforms were detected using the disclosed primers (e.g., page 5). Statistical analysis was performed (e.g., pages 5-6).

The claims are broader than the method disclosed in the declaration. The claims are not limited to the isolation of MNC from blood and are not limited to detecting mRNA expression. The claims encompass determining the expression of any manganese superoxide dismutase gene, which the specification defines as "enzymes which catalyze the decomposition of superoxide free radicals to form hydrogen peroxide, and in particular the enzymes which constitute enzyme class 1.15.1.1" (paragraph bridging pages 14-15). The enzymes of this class are not limited to manganese-containing superoxide dismutase enzymes, or the human SOD2 gene that is capable of being amplified by primers of SEQ ID NOS: 1 and 2 of the present specification. Furthermore, the claims encompass the use of any primers to detect expression of thioredoxin reductase 1 genes, and glutathione peroxidase 1 genes. Moreover, the claims encompass the use

of any further cell-containing fraction of the body fluid or any comparable biological sample for comparison purposes.

For analysis of the mRNA expression data, the declaration divides the human subjects into four groups: A, B, C and D. Group A includes subjects with a tumor, but prior to surgery. Group B includes subjects without a tumor. Groups C and D include subjects with a previous clinical diagnosis of prostate cancer and surgery, but differences in the effects of surgery to reduce the load of cancer cell clusters (CCC) (e.g., page 6).

Section 5.1 of the declaration provides an analysis of the data for early detection of primary prostate cancer. The data shows that the quantitative measurement of SOD2 mRNA, GPX1 mRNA and TXNRD1 mRNA in circulating cancer cell clusters is a reliable method for the prediction of prostate primary tumor in patients with a serum PSA level between 4 and 10 ng/ml. As discussed above, the present claims are much broader in scope with respect to the method steps of analyzing gene expression. Furthermore, the present claims are directed to the diagnosis of any tumor (e.g., claims 14 and 15). Moreover, the claims do not limit the test subjects to humans with a serum PSA level between 4 and 10 ng/ml. The specification does not disclose the selection of subjects for tumor diagnosis based upon a serum PSA between 4 and 10 ng/ml.

Section 5.2 of the declaration provides an analysis of the data for the prognosis of the disease course, i.e., relapse-free survival (RFS). The declaration states that predictive values were calculated from the 95% CI threshold values of at risk patients (group D). The declaration shows that the relapse-free survival for patients overexpressing SOD2 and GPX1 is shorter than for patients not overexpressing SOD2 and GPX1. As discussed above, the present claims are

much broader in scope with respect to the method steps of analyzing gene expression. Furthermore, the present claims are directed to estimating the risk to develop a metastasis or recurrence for any type of cancer (e.g., claims 16 and 17). Moreover, the claims do not limit the genes for determining prognosis to SOD2 and GPX1. The claims encompass the use of any two genes selected from manganese superoxide dismutase genes, thioredoxin reductase 1 genes, and glutathione peroxidase 1 genes.

Section 5.3 of the declaration provides an analysis of the data for the prediction of distant and local relapse. This study included 64 patients with local and/or distant relapse and the 77 patients of Group C. The declaration states that expression of SOD2 and GPX1 was elevated throughout the postsurgical period and remained elevated until relapse tumor formation if no other treatment was give. Section 5.3.1 of the declaration provides an analysis of the data for distant relapse. This study included 51 patients with distant relapse and the 77 patients without relapse (Group C). The declaration states that predictive values were calculated from the 95% CI threshold values of at risk patients. SOD2 and GPX1 were found to predict distant tumor formation, primarily bone metastases. Section 5.3.2 of the declaration provides an analysis of the data for local relapse. This study included 49 patients (40 with bone metastases and 9 patients with local relapse only). The declaration states that distant relapse was predicted with GPX1 and SOD2, whereas local relapse was predicted with GPX1, SOD2 and TXNRD1. The declaration states that the elevated expression of TXNRD1 in the case of local relapse allowed differentiation of local from distant relapse (e.g., page 15). However, the prediction of distant and/or local relapse is not disclosed in the present specification, and the specific gene

combinations of genes capable of being used to differentiate between the two conditions were not disclosed.

In summary, the declaration states that predicting the primary tumor, as well as local relapse, involved the evaluation of all three genes. For disease prognostication (relapse-free survival) as well as for predicting bone metastases, SOD2 and GPX1 were the lead markers, and the correctness of prediction amounts to values between 70% and 90%. The declaration evidences that practicing the method as claimed requires information that was not disclosed in the application as of its filing date. Therefore, the declaration clearly evidences that additional experimentation would be required to use the claimed method for the diagnosis of a tumor (or determining the presence of a tumor) and for estimating the risk to develop metastasis or a recurrence. The skilled artisan would not have been enabled by the specification to diagnose a tumor or determine the risk to develop a metastasis or recurrence for any cancer at the time of filing.

The declaration notes that the studies were carried out on blood with respect to prostate cancer, but states, "it can reasonably be expected that essentially the same method can be applied to bone marrow and other cancer types." The declaration does not provide evidence that bone marrow or other cancer types can be used in the analysis. Further experimentation would be required to determine the appropriate comparison samples and combinations of genes to diagnose a tumor and to predict the risk of metastasis or recurrence for another sample type or cancer type.

Thus, in view of the evidence considered as a whole, it is concluded that the declaration fails to establish that one of skill in the art would have been enabled to make and use the invention presently claimed without undue experimentation.

Response to Arguments - 35 USC § 112

The rejection of claims 5, 7 and 13 under 35 U.S.C. 112, first paragraph, is moot in view of Applicant's cancellation of the claims in the reply filed 9/15/2008.

With respect to the rejection of claims 1-4, 6, 11, 12 and 14-25 under 35 U.S.C. 112, first paragraph, Applicant's arguments filed 9/15/2008 have been fully considered but they are not persuasive.

The response notes that the amended claims are drawn to a method for investigating blood or bone marrow for disseminated cancer cells. The specification teaches that disseminated cancer cells are expected to be present in the blood and bone marrow (e.g., pages 5-6). The response asserts that the method is enabled for investigating bone marrow in addition to blood. The response specifically points to section 5.4 of the declaration of Professor Giesing. This section of the declaration notes that the experimental data presented in the declaration is only for blood. However, it is the opinion of Professor Giesing that "it can reasonably be expected that essentially the same method can be applied to bone marrow and other cancer types." Seven et al (1999, of record) teach that the levels and inducibility of antioxidant enzymes SOD, GSH, Px and catalase vary for different tissues (e.g., page 372, left column, 4th full paragraph). Further Seven et al teach that the inconsistency of data with regard to the oxidation system and its components may be due to different cancer types, cancer grades or other characteristics of the

patients examined (e.g., page 372, left column, last full paragraph). Given the unpredictability in the area of the invention, one would not have reasonably expected to extrapolate the results provided in the present specification to the use of any body fluid, and any comparable biological sample. Furthermore, one could not extrapolate the results disclosed in the present specification to the results disclosed in the declaration, and the declaration provides evidence that further experimentation would be required to enable other embodiments that fall within the scope of what is claimed.

The response notes that the claimed method now includes the use of a reference sample, which is "a further cell-containing fraction of the body fluid of or a comparable biological sample." The response notes that the reference sample is defined as a further cell-containing fraction of **the** body fluid or of a comparable biological sample. Thus, the further cell-containing fraction is derived from the same body fluid as the cell-containing fraction or is derived from a comparable biological sample. Accordingly, the claims broadly encompass the use of essentially any cell-containing fraction as a reference. Given the variable expression of antioxidant enzymes in different tissues, it would be unpredictable to use any cell sample as a comparison or any cell-fraction from the body fluid. The assay requires an increase in expression of each gene relative to the further cell-containing fraction. If one uses a cell-fraction with high levels of expression, then more false negative results will be obtained. If one uses a cell-fraction with low levels of expression, then more false positive results will be obtained. The reliability of each test must be experimentally validated, and the present specification only provides data for the use of CD45 positive lymphocytes isolated from human blood as a comparison sample.

The response notes that the specification teaches that the test principle is based on determining whether enrichment of cancer cells is associated with a measurable increase in MNSOD, TXNRD, and GPX expression. The specification states that the ratio of the expression measured in the test cell mixture to the expression measured in the comparison cell mixture is decisive (page 29, lines 33-39). The response asserts that the specification teaches that it is sufficient for the method if the proportion of cancer cells is significantly higher in the test cell mixture than in the comparison cell mixture (e.g., page 29, lines 1-6). The response asserts that it will be obvious to a person of ordinary skill in the art that 1) the comparison cell mixture must not necessarily be derived from the same body fluid of the same individual as the test cell mixture, and 2) the comparison cell mixture must not necessarily be derived from the same body fluid of the same individual as the test cell mixture. These arguments are not found persuasive. The claims require a further cell-containing fraction of the body fluid of the test subject or a further cell-containing fraction of a comparable biological sample, which may be from the test subject or a control subject. The working example in the present specification teaches the use of both a CD45 lymphocyte containing fraction from peripheral blood of the test subject, and CD45 lymphocyte containing fractions from peripheral blood of a control subject in order to make the necessary comparisons for the identification of disseminated cancer cells in the peripheral blood of the test subject. While comparisons other than the ones disclosed in the present specification may be used, further experimentation would be required to determine which comparisons provide a valid indication of the presence of disseminated cancer cells, the diagnosis of a tumor, and the risk to develop a metastasis or recurrence. This type of experimentation is not routine in the art. It requires a large amount of inventive effort and would be undue.

The response asserts that Seven et al does not evidence the unpredictability in the art, because Seven et al are concerned with antioxidant activity in blood plasma and erythrocytes. The response asserts that the present invention is concerned with the determination of antioxidant enzymes in disseminated cancer cells, specifically cancer cells found in the mononuclear cell fraction, in contrast to the erythrocytes. These arguments are not found persuasive. The claims are drawn to the use of a body fluid, which is blood. The claims are not limited to the use of a mononuclear cell fraction of blood. Erythrocytes are a component of blood, and the claims encompass the use of these cells in the method. Furthermore, Seven et al teach more than antioxidant activity in blood plasma and erythrocytes. Seven et al state the following at page 372:

> Several reports have found antioxidants and enzymes related to the antioxidant function at increased levels in serum, erythrocytes, or tumor tissue of early stage cancer patients when compared with controls (9,29). The high levels of antioxidants were suggested to be a self-serving feature developed by tumor cells, eventually providing a selective advantage for proliferation (29).
>
> In line with our findings, Gerber *et al.* (29) reported significant higher plasma vitamin E levels in breast cancer. In contrast with these studies, Palan *et al.* (5) reported decreased plasma levels of antioxidants in cervical cancer patients compared with normal subjects. Lower plasma vitamin C and E levels were observed in malign breast tumors compared with controls (21). The controversial findings in the literature related to lipid peroxidation and antioxidant status in cancer may arise from the type of cancer/tissue studied. The adaptive antioxidant response against oxidant stress is thought to be tissue specific. The constitutive levels and the inducibility of the antioxidant enzymes SOD, GSH Px, and catalase vary for different tissues.
>
> Oxidation system along with its components is complex and the inconsistency of the data from the literature is possibly because of different cancer types, cancer grades, or other characteristics of the patients examined.

Thus, the teachings of Seven et al are directed to more than antioxidant activity in blood plasma and erythrocytes. Seven et al provide evidence of the unpredictable nature of the invention. One

skilled in the art could not readily anticipate the effect of a change in the subject matter with regard to the different uses of the method or with regard to varying the method steps from those specifically disclosed in the specification. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Thus, specific guidance is what is needed rather than general guidance (e.g., a statement than any comparison could be used).

The response notes that the amended claims are now directed to the determination of expression of at least two genes selected from manganese superoxide dismutase, thioredoxin reductase 1, and glutathione peroxidase 1. At page 10, the response asserts that the person of average skill in the art clearly distinguished between a manganese superoxide dismutase (superoxide dismutase 2) and a CuZnSOD (superoxide dismutase 1). The response notes that both enzymes catalyze the same process: the decomposition of superoxide radicals to form hydrogen peroxide and belong to the same enzyme class, 1,15,1,1; however, they are distinct enzymes. The response asserts that the paragraph bridging pages 14-15 of the present application does not mean that the manganese superoxide dismutases of the present invention encompass CuZnSOD. These arguments are not found persuasive. The specification explicitly defines the term "manganese superoxide dismutase (MNSOD for short)" to mean "enzymes which catalyze the decomposition of superoxide free radicals (O_2^-) to form hydrogen peroxide (H_2O_2)." See page 14, lines 35-38. Although one skilled in the art would distinguish between MNSOD and CuZnSOD, Applicant has explicitly defined the term "manganese superoxide dismutase" to encompass both MNSOD and CuZnSOD. As acknowledged in the reply, both

enzymes catalyze the decomposition of superoxide free radicals (O_2^-) to form hydrogen peroxide (H_2O_2). Thus, the claims broadly encompass determining the expression of a gene encoding any enzyme that catalyzes the decomposition of superoxide free radicals (O_2^-) to form hydrogen peroxide (H_2O_2).

With respect to the different isoforms of MNSOD, TXNRD1 and GPX1 whose expression may be determined in the claimed method, the response asserts that Applicants have checked which transcript variants are detected when the disclosed primers and probes are used. This evidence is presented in the declaration of Professor Giesing. Thus, the response asserts that these results corroborate that the specification is enabling even when it comes to the detection of transcript variants. Further, the response asserts that it would be obvious to a person of ordinary skill in the art to use appropriate primer and probe designs if one of said variants is to be differentially detected. These arguments are not found persuasive. The declaration does not provide evidence that the expression levels of each of the transcript variants are proportional or that each transcript variant expression level is predictive in the claimed method. Thus, one could not reasonably extrapolate from the use of the primers and probes disclosed in the present specification (and used in the declaration) other primers and probes that would necessarily give the same result with regard to the differential expression observed in the presence of disseminated cancer cells.

The response notes that the claims have been amended to relate to diagnosis of a tumor rather than early diagnosis of a tumor. This amendment does not overcome the rejection, because the specification does not teach the reliable classification of subjects as having or not

having a tumor based upon the expression of at least two genes selected from manganese superoxide dismutase genes, thioredoxin reductase 1 genes, and glutathione peroxidase 1 genes.

With respect to classifying subjects as at risk or not at risk to develop a metastasis or recurrence, the response points to the data described in Professor Giesing's declaration to corroborate that the method of the present invention is suitable for predicting not only the primary tumor but also relapse-free survival and the risk of developing a distant or local relapse. This argument is not found persuasive, because the data described in the declaration are not commensurate in scope with the claimed invention, and include elements not disclosed in the originally filed specification such as the selection of individuals for diagnosis of prostate cancer based upon a serum PSA level between 4 to 10 ng/ml, and the particular gene combinations to predict the presence of distant metastases or local metastases, for example.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Response to Arguments - 35 USC § 102

The rejection of claims 1, 3 and 11 under 35 U.S.C. 102(b) as being anticipated by Seven et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 9/15/2008.

The rejection of claims 1, 3 and 11 under 35 U.S.C. 102(b) as being anticipated by Kizaki et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 9/15/2008.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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